CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-335

PHARMACOLOGY/TOX REVIEW(S)

MEMORANDUM

Date: May 7, 2001
From: John K. Leighton, Ph.D., DABT
Supervisory Pharmacologist, HFD-150
To: File for NDA #21-335
Re: Approvability for Pharmacology and Toxicology
Gleevec™, imatinib mesylate

Gleevec, or imatinib mesylate (also known as STI 571), is a protein tyrosine kinase inhibitor. Novartis is seeking approval for Gleevec for the treatment of chronic myeloid leukemia in the blast crisis, accelerated phase, or in the chronic phase after failure of interferon-alpha therapy. For the pharmacology and toxicology section of this NDA, Novartis conducted studies examining acute and chronic toxicology (up to 13 weeks in the dog, 26 weeks in the rat and 39 weeks in monkeys), pharmacology, pharmacokinetics, and reproductive toxicology studies in rats and rabbits (ICH A-B and C-D). The high dose used in the chronic and reproductive toxicology studies was approximately equivalent to the intended clinical dose on a body surface area basis. It is not certain that the doses used in the toxicology studies fully defined the spectrum of potential toxicity, particularly in the monkey studies. A panel of genotoxicology studies was conducted. Included in the genotoxic evaluation were studies examining intermediates in the manufacturing process. Dr. Kimberly Benson, after a review of the studies provided by the applicant, concluded that the toxicology and pharmacology studies supported the approval of imatinab mesylate. I concur with her conclusions.

Carcinogenicity studies were not conducted for this NDA and are not necessary to support approval for the intended indication.

A detailed labeling review was provided by Dr. Benson and I agree with the requested changes.

As noted by Dr. Benson, imatinab mesylate undergoes rapid and extensive metabolism in all species tested. Deviation of AUC from dose proportionality was observed in rats and monkeys. Thus, the use of body surface area rather that AUC was used in comparison of toxicological findings.

Recommendations: The pharmacology and toxicology data supports approval of this NDA. However, the toxicology studies may not sufficient to support substantial changes in the dosing regime or additional indications.

In addition, the following changes to the label are suggested in the respective sections.

OVERDOSAGE

DRAFT LABELING

NURSING MOTHERS

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and/or its metabolites were extensively excreted in milk. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking GLEEVEC.

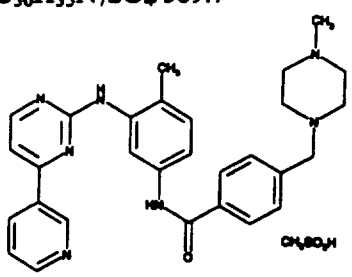
Outstanding issues: Liver and possibly renal toxicity and the potential for drug-related opportunistic infection observed in animal studies should be discussed in the label given the short follow-up of patients in clinical trials. No additional animal studies are necessary to support the NDA for the proposed indication. The potential for liver toxicity will be assessed as a phase 4 commitment. It is suggested that language be included in the PRECAUTIONS section of the label to describe these animal findings.

Original NDA
CC: /Div file
/KBenson
/AStaten

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	21-335
Review number:	1
Serial number/date/type of submission:	000/27 February 2001/NDA
Information to sponsor:	Yes (X) No ( )
Sponsor and/or agent:	Novartis Pharmaceuticals Corporation
Manufacturer for drug substance :	Novartis Ringaskiddy Ltd.
Reviewer name:	Kimberly A. Benson, Ph.D.
Division name:	Division of Oncological Drug Products
HFD #:	150
Review completion date:	4 May 2001

Drug:

Trade name:	Gleevec™
Generic name:	Imatinib mesylate (Pending)
Code name:	STI571; CGP 57148B
Chemical name:	4-[4-(Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonate
CAS registry number:	220127-57-1 [152459-95-5 for the free base]
Mole file number:	None
Molecular formula/ weight:	$C_{30}H_{35}N_7SO_4$/589.7
Structure:	

Relevant INDs:

Drug class: Protein-tyrosine kinase inhibitor

Indication: For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy.

Clinical formulation:

Ingredient	Amount (mg)
STI571 mesylate	
Microcrystalline cellulose	
Crospovidone	
Silica, colloidal anhydrous/ Colloidal Silicon Dioxide	
Magnesium stearate	

Route of administration: Oral tablets

Proposed use: For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy. The recommended dosage is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose should be administered orally, once daily with a meal and a large glass of water. Treatment should be continued as long as the patient continues to benefit. Dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Gleevec® (imatinib mesylate) is an inhibitor of protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. The inhibition of Bcr-Abl kinase is important, as it is believed to play a role in the deregulated myeloid cell proliferation that is the hallmark of chronic myeloid leukemia (CML). The Philadelphia chromosome arises from a reciprocal translocation between chromosomes 9 and 22. Replacement of the first exon of c-Abl with sequences from the Bcr gene result in a Bcr-Abl fusion gene with a 210-kD protein product that exhibits enhanced protein-kinase activity and is present in 95% of CML.

Studies were conducted in the mouse, rat, dog, rabbit, monkey, and cellular assay systems to explore the pharmacology, general toxicology, genotoxicity and reproductive effects of imatinib mesylate. Where possible, the animals were administered the drug orally, the route used in the clinic. Long-term studies were conducted in the rat and monkey, for 26 and 39 weeks, respectively.

Safety evaluation:

The highest clinical dose of Gleevec® proposed for the indication CML is 800 mg/day, or 471 mg/m^2/day. Repeated oral dosing of imatinib has been tolerated well in the rats, dogs and monkeys. Doses of 90 mg/m^2/day in the rat, 600 mg/m^2/day in the dog and 360 mg/m^2/day in the monkey were not severely toxic when administered daily for periods of 13-39 weeks. Target organs in the animal studies are epithelial and glandular tissues.

The hematopoietic system was affected by imatinib doses $\geq$ 120 mg/m^2/day in the rat, $\geq$ 200 mg/m^2/day in the dog, and $\geq$ 900 mg/m^2/day in the monkey. The major hematological effect involved decreases in red cell parameters. White blood cells were decreased at this dose in the dog and at higher doses in the rat, $\geq$ 360 mg/m^2/day. The myelosuppression is believed to be a direct pharmacological effect of imatinib.

Lymphoid tissues were effected by imatinib administration of doses $\geq$ 1200 mg/m^2/day in the rat and $\geq$ 200 mg/m^2/day in the dog. Histological effects seen following imatinib administration included lymphoid atrophy and lymphoid depletion. In the monkey, these effects were not seen. Treatment with imatinib did appear to decrease the ability to fight off the subclinical malarial infection commonly found in this species of monkey. The hyperplasia of the spleen seen in these monkeys, at doses $\geq$ 180 mg/m^2/day, was attributed to the infection. The sponsor hypothesizes that the recrudescence of the malarial infection is related to the PDGF inhibition of imatinib. PDGF is involved in the signaling pathway for induction and expression of inducible nitric oxide synthetase, which is believed to have an antiparasitic function against malaria. PDGF inhibition by imatinib may have inhibited the formation of nitric oxide (NO) and blocked the inhibitory effects of NO on parasitic proliferation. Clinically, no increased incidence of opportunistic infections has occurred to date. It is still important to consider that the effect of imatinib on lymphoid tissue coupled with the mild myelosuppression may contribute to potential

interactions with normal immune responses. The results of the 39-week monkey study may indicate such an interaction.

Toxicity of the kidney was seen in the rat 13-week study, at doses $\geq$ 36 mg/m^2/day. Histological changes in the kidney were primarily seen in the high dose of 360 mg/m^2/day. But hyperplasia of the transitional renal epithelium was connected to hyperplasia in the urinary bladder, which was seen at all doses $\geq$ 36 mg/m^2/day, in a dose-dependent manner. These histological changes were not accompanied by changes in serum and urinary parameters of kidney function. A repeat 13-week study in the rat, with doses up to 60 mg/m^2/day, did not replicate these findings. However, administration of imatinib to rats for 26 weeks, yielded renal pelvic epithelial hyperplasia in 15% of the 90 mg/m^2/day rats and nearly 60% of the rats dosed with 300 mg/m^2/day. At 2000 mg/m^2/day, transitional cell hyperplasia was also seen in the dog after 2 weeks. In a 2-week monkey study, the high dose animals were treated with 1800 mg/m^2/day for six days, before clinical signs led to a reduction to 1200 mg/m^2/day for the remaining eight days. In these high dose animals, imatinib led to focal mineralization and dilatation of the renal tubules and tubular nephrosis. The two monkeys treated at this dose also had increased BUN and creatinine. One monkey was euthanized with morbidity attributed to nephrosis. Administration of imatinib to monkeys, at doses up to 960 mg/m^2/day for up to 39 weeks, did not yield changes in clinical chemistry indicators of renal function, and only minimal histological changes in the kidney. The lack of clinical chemistry findings, however, does not preclude ongoing histological alterations of the kidney and bladder. Often these parameters are not altered until considerable renal damage has occurred. In addition, the doses used in the long-term monkey studies may not have been high enough to fully explore the renal toxic effects of imatinib.

Toxicity of imatinib on the gastrointestinal tract was evident in the dog and monkey studies. In the dog, repeated oral dosing for 13 weeks at doses $\geq$ 60 mg/m^2/day caused significant diarrhea. Emesis was seen at doses $\geq$ 600 mg/m^2/day administered for 2 weeks in the dog, and in the monkey at doses $\geq$ 900 mg/m^2/day following at least 13 week administration. Histopathological results showed intestinal mucosa atrophy, GI epithelial vacuolar degeneration and single cell necrosis following administration of $\geq$ 200 mg/m^2/day of imatinib for 2 – 13 weeks and after 2 weeks of 3600 mg/m^2/day to the rat. Emesis was seen only following oral administration, not i.v. It is, therefore, most likely a local irritation effect of imatinib that causes emesis in the monkey and dog.

The testis and ovary are also target organs of imatinib toxicity. Reduced spermatogenesis and testis weights were noted in the dog at $\geq$ 600 mg/m^2/day. Decreased sperm motility and testicular weights were seen in rats at doses of 360 mg/m^2/day. In the monkey, decreased testis weights and testicular immaturity or degeneration was seen at doses $\geq$ 180 mg/m^2/day. Ovaries of rats treated with 300 mg/m^2/day imatinib for 26 weeks. It is believed that these findings are a direct pharmacological effect of imatinib, as c-Kit, a tyrosine kinase, is implicated in spermatogonial proliferation and ovarian follicle development.

Toxicity in the liver was evident by a slight increase in transaminases and slight decreases in cholesterol, triglycerides and albumin in the rat and dog. Indications of liver effects of imatinib were not seen in the monkey studies. In the rat, histopathological changes in the liver were not seen in conjunction with the noted clinical chemistry changes. The dog, however, had

more severe liver toxicity from imatinib. Clinical chemistry changes were seen at doses ≥ 600 mg/m^2/day. Histological changes included mild multifocal hepatocellular necrosis, single cell necrosis in the bile duct, and bile duct hyperplasia, and were seen most frequently at doses ≥ 2000 mg/m^2/day. The bile duct hyperplasia was still present following the four-week recovery period and was associated with peribiliary fibrosis. Further assessment is planned by the sponsor to determine the progression of this toxicity and to further assess the potential for reversibility. However, no studies are outlined for further examination of this toxicity in the dog.

It should be noted that the doses of imatinib used in the long-term and reproductive toxicity studies in laboratory animals did not exceed the proposed clinical dose, based on body surface area. In many studies, the highest dose tested in the animals was approximately equal to the proposed clinical dose. Studies using higher doses, to better determine the margin of safety with long-term repeated oral administration, may have shed more light on the toxicity of imatinib, especially the potential for renal and hepatic toxicity.

Safety issues relevant to clinical use:

The liver toxicity was seen most prominently in the dog. The histopathological evidence of toxicity occurred along with elevated transaminases. A slight elevation in liver function tests was also seen in the rat, though without evidence of histological toxicity. The animal data illustrates the importance of monitoring liver function while taking Gleevec®. The potential for Gleevec® to impact the host immune response, as evident by the recrudescence of malarial infection in monkeys treated with imatinib, warrants consideration in the clinical setting. The renal toxic effects of Gleevec® are not fully understood. The monkey data shows that there may be kidney toxicity with doses of imatinib approximately 3-4 fold higher than the 800 mg dose in the human population, based on body surface area.

Other clinically relevant issues:

The carcinogenicity of imatinib mesylate has not been evaluated. Studies in rats and rabbits clearly show imatinib mesylate is significantly fetotoxic, evidenced by increased post-implantation fetal loss. Teratogenic potential of imatinib was demonstrated in rat studies, at doses approximately equivalent to the highest clinical dose of 800 mg, based on body surface area. Exencephaly, encephalocele and protruding tongue were noted in the surviving fetuses. Numerous skeletal malformations were seen in the offspring at this dose. Significant decreases in fetal body weight were also seen in the surviving fetuses exposed prenatally to a dose approximately equal to the highest clinical dose.

Because of the reproductive toxicity seen in the animal studies, assuring that a patient is not pregnant prior to starting Gleevec® therapy, as well as advising the patient to take precautions to avoid pregnancy during therapy, is essential. Women should also be told to not breastfeed while taking Gleevec®.

Conclusions:

There are sufficient animal studies, with the appropriate route of administration, long-term repeated exposures, and adequate doses compared to the proposed human dose, to explore the potential toxicities of Gleevec®. Most of the toxicities seen in the laboratory studies were to

be expected, based on the pharmacological actions of the drug. The target organs are epithelial and glandular tissues. The liver toxicity is a major concern, based on the lack of reversibility in the dog model and one patient in the clinical trials that died from liver toxicity, although there was concomitant use of other hepatotoxins.

Communication review:

Labeling review:

Label review will follow.

RECOMMENDATIONS:

Internal comments:

External recommendations (to sponsor):

The liver toxicity seen in the dog is of concern. It would be beneficial if the sponsor follows through on the intent to further explore this toxicity.

Draft letter content for sponsor (if not same as above):

Future development or issues:

None

Reviewer signature: /S/

Team leader signature: /S/

cc: /Div file
/JLeighton
/AStaten

Memorandum of non-concurrence:

Not applicable

Addendum to review:

None

Studies reviewed within this submission:

Pharmacology

Report PKF-98-02342: CGP 57148B: A potent protein-tyrosine kinase which inhibits PDGF receptor and c-Kit mediated signal transduction. Volume 1.9, page 5-58.
RD-2000-01471: ST1571: an ATP-competitive inhibitor of the c-AbI protein-tyrosine kinase. Volume 1.9, page 5-75.
PKF-99-01118: Acute and maximally tolerated dose of ST1571 (CGP 5714813) in mice. Volume 1.9, page 5-89.
RD-2000-01407: Pharmacological profile of CGP 74588A: in vitro studies of the methanesulfonate salt of CGP 74588, a major metabolite of ST1571. Volume 1.9, page 5-103.
RD-2000-00329: ST1571 does not decrease the tolerability of mice to conventional cytotoxic anticancer agents. Novartis Report, 2000. Volume 1.10, page 5-1.

Pharmacokinetics/Toxicokinetics

DMPK(US) R98-1782: CGP 5714813: A 13-week oral (gavage) toxicity study in rats. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in plasma. Volume 1.31, page 5-322.
DMPK(US) R99-683: CGP 5714813: A 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of ST1571 in plasma. Volume 1.31, page 5-341.
DMPK(US) R99-039: CGP 5714813: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in monkey plasma. Volume 1.32, page 5-181.
DMPK(CH) R00-097: Galactogenic transfer, kinetics and metabolism in milk and plasma after single peroral administration of ^{14}C-labeled ST1571 (100 mg/kg as the methanesulfonic acid salt) to lactating rats. Volume 1.32, page 5-286.
DMPK(CH) R00-1004: Quantitative whole-body autoradioluminography in female normal and bearing C6 tumors BALB/c nu/nu mice following a 50 mg/kg po dose of [^{14}C]ST1571. Volume 1.33, page 5-26.

Safety Pharmacology

DP00-R07: STI571: Safety pharmacology study - Effects on acetic acid-induced stretching, convulsions, and gastrointestinal transit. Volume 1.9, page 5-304.

Toxicology

Test 007033: ST1571: 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. Report DMPK (US) R99-683. Volume 1.15; page 5-1.
987003: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period. Volume 1.22, page 5-1.
Test 007048: ST1571: 39-week oral gavage (b.i.d.) toxicity study in monkeys with a 4-week recovery period. Volume 3.1, page 1.

Genetic Toxicology

NOTOX 271608: Evaluation of the mutagenic activity of ST1571 D9 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). Volume 1.27, page 5-177.

NOTOX 272036: Evaluation of the mutagenic activity of ST1571 D6 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). Volume 1.27, page 5-203.

001815: Mutagenicity test using *Salmonella typhimurium* (Batch control). Volume 1.27, page 5-229.

001889: Oral bone marrow micronucleus test in rats. Volume 1.27, page 5-278.

001864: Mutation assay at the thymidine kinase locus of L5178Y mouse lymphoma cells. Volume 1.27, page 5-306.

Test 946215: CGP 53715: Gene mutation test with Chinese hamster cells V79. Volume 1.27, page 5-257.

Reproductive Toxicology

Test 974046: CGP 571488: An oral study for effects on fertility and early embryonic development in rats. Novartis Pharmaceuticals Corporation, Summit, New Jersey, 22 May 99. Volume 1.28; page 5-1.

Test 966086:CGP 5714813: A Study for Effects on Embryo and Fetal Development in Rats. Novartis Crop Protection, Toxicology/Experimental Toxicology, 4332 Stein, Swit. 25 Aug 97. Volume 1.29; page 5-1.

Test 966088: GP 5714813: A Study for Effects on Embryo and Fetal Development in Rabbits. Novartis Crop Protection, Toxicology/Experimental Toxicology, 4332 Stein, Switz. 25 Aug 97. Volume 1.30; page 5-1.

Special Toxicology

Test 001091: ST1571 Single-dose oral mechanistic toxicity and safety pharmacology study in dogs. Novartis Pharma AG, (Basel), Toxicology/Pathology report, 28-Dec-00. Volume 1.27; page 5-100.

Studies <u>not</u> reviewed within this submission:

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pages of trade

secret and/or

confidential

commercial

information

Introduction and drug history:

Gleevec® (imatinib mesylate) is an inhibitor of protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. The inhibition of Bcr-Abl kinase is important, as it is believed to play a role in the deregulated myeloid cell proliferation that is the hallmark of chronic myeloid leukemia (CML). The Philadelphia chromosome arises from a reciprocal translocation between chromosomes 9 and 22. Replacement of the first exon of c-Abl with sequences from the Bcr gene result in a Bcr-Abl fusion gene with a 210-kD protein product that exhibits enhanced protein-kinase activity and is present in 95% of CML.

Imatinib has been investigated for toxicological effects in numerous studies in mice, rats, rabbits, dogs and monkeys. Target organs for drug toxicity in these animals include the liver, hematopoietic system, lymphoid tissue, gastrointestinal tract, testes and ovaries. In both the rat and rabbit, imatinib is fetotoxic when administered during gestation. In the rat the drug was also a teratogen, primarily causing malformations of the skeletal system. In genotoxicity assays, two intermediate products in the drug product manufacturing process, that are present in the final product, were positive mutagens. Imatinib was positive for clastogenicity in the Chinese hamster ovary cell assay.

Gleevec® is currently in clinical trials under IND[ ]. As of March 2000, over 1046 adults had been treated with Gleevec® at doses ranging from 25 to 1000 mg/day. Mild to moderate nausea, periorbital edema and mild to moderate musculoskeletal symptoms were the most common adverse events reported, and all appeared to have a dose-response relationship with Gleevec®. Serious adverse events were reported 191 times, 51 of which had a suspected causal relationship to the test drug. These events occurred in 0.3-1% of patients and fell into 5 broad categories: rash, liver function test abnormalities, myelosuppression, gastrointestinal hemorrhage, and edema and fluid retention (sometimes accompanied by renal failure).

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TABLE OF CONTENTS

PHARMACOLOGY:

Primary pharmacodynamics:

Mechanism of action:

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits PDGF, c-Kit and Abl.

Drug activity related to proposed indication:

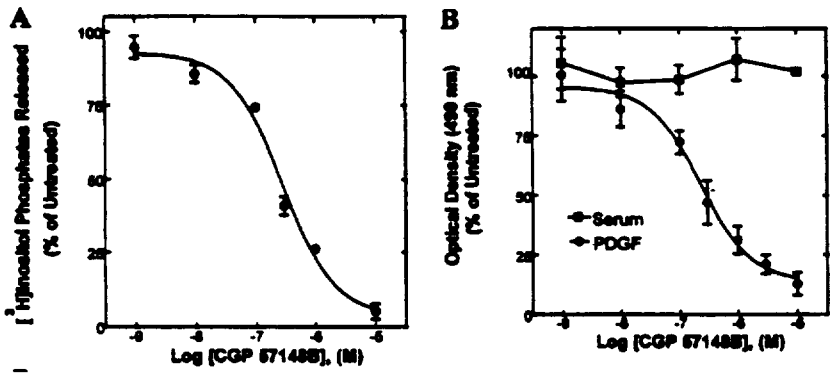
Report PKF-98-02342: CGP 57148B: A potent protein-tyrosine kinase which inhibits PDGF receptor and c-Kit mediated signal transduction. Volume 1.9, page 5-58.

Conducted by Novartis AG, Switzerland: CGP 57148B was analyzed *in vitro* for inhibition of a panel of protein-tyrosine kinases. CGP 57148B was found to have no inhibitory effect on the ligand-stimulated Flt-3 tyrosine kinase activity in myeloid M1 cells. The following table shows weak to no inhibition by CGP 57148B of Kdr, Flt-1, Tek, FGFR-1 and c-Met tyrosine kinases *in vitro*.

Stimulation of both the α and β PDGF receptors was inhibited by CGP 57148B in Swiss 3T3 cells, with and IC_{50} value of approximately 0.1 μM.

MO7e cells were used to determine the effects of CGP 57148B on the phosphorylation of two MAP kinases, $pp44^{erk1}$ and $pp42^{erk2}$, in response to stem cell factor (SCF) stimulation of c-Kit. The SCF-induced activation of these MAP kinases was inhibited with an IC_{50} value between 0.1 - 1 μM. PDGF BB-mediated activation of MAP kinases was also inhibited by CGP 57148B in rat A10 smooth muscle cells.

In rat A10 smooth muscle cells, CGP 57148B inhibited PDGF-mediated [^{3}H]inositol phosphate release. It also inhibited PDGF-BBR 3464 stimulated A10 cell proliferation, but had no effect on serum induced cell proliferation.



RD-2000-01407: Pharmacological profile of CGP 74588A: in vitro studies of the methanesulfonate salt of CGP 74588, a major metabolite of ST1571. Novartis Report. Volume 1.9, page 5-103.

Conducted by Novartis Pharma AG, Switzerland. STI571 is also known as CGP 57148B. CGP 57148 is the main metabolite of STI571. CGP 57148A, the methanesulfonate salt of CGP 57148, was analyzed *in vitro* for inhibition of a panel of protein-tyrosine kinases. Like STI571, CGP 57148A was found to inhibit c-Abl and c-Kit tyrosine kinases. Weak or no inhibition by was seen of Kdr, Flt-1, Tek, and c-Met tyrosine kinases *in vitro*.

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Table 1.

RD-2000-01471: ST1571: an ATP-competitive inhibitor of the c-Abl protein-tyrosine kinase. Novartis Release Ready Report. Volume 1.9, page 5-75.

Conducted by Novartis Pharma AG, Switzerland. Kinetic constants were determined for the Abl tyrosine-protein kinase. The mode of inhibition by STI571 and its dissociation constant were also determined. From the data obtained, it appears that STI571 has an ATP-competitive mode of inhibiting c-Abl kinase. The figure below shows that increasing concentrations of STI571 did not affect the Vmax of ATP (as indicated by the Y-axis intercept) but increased the Km for ATP (slope of the line), indicative of a competitive inhibition of ATP by STI571, with a Ki of 85 ± 19 nM.

RD-2000-00329: ST1571 does not decrease the tolerability of mice to conventional cytotoxic anticancer agents. Novartis Report, 2000. Volume 1.10, page 5-1.

Conducted by Novartis Pharma AG, Switzerland. STI571 was administered orally to female BALB/c mice alone or in combination with near MTD of standard chemotherapeutic agents doxorubicin, 5-fluorouracil, cisplatinum, and Taxol®. Body weights and mortality were measured for 14 days following treatment single treatment with STI571, the conventional agent, or the conventional agent with 100, 200 or 300 mg/kg STI571. STI571 was tolerated better than the conventional agents, based on body weight changes in the mice. The addition of STI571 to the regimen did not appear to significantly worsen the weight loss seen with the conventional agents. Mortalities in the STI571 + cisplatinum test did occur only in the combination groups – 1/5 for each of the three combinations. But no body weight effects of the combination were evident with cisplatinum.

Pharmacology summary:

Imatinib mesylate and the methanesulfonate of its major metabolite were both assayed for *in vitro* inhibition of purified tyrosine-protein kinases. Various cell culture assays were also used to determine the inhibitory effects of imatinib. Inhibition was seen with α and β PDGF receptors, c-Kit and Abl tyrosine kinase assays. Activation of PDGF receptors lead to inositol release and MAP kinase activation in MO7e cells, and cell proliferation in A10 rat aorta smooth. Imatinib inhibited these PDGF-induced effects in a dose-dependent manner. Imatinib mesylate appears to competitively inhibit ATP binding with regard to the Abl tyrosine kinase.

Pharmacology conclusions:

Imatinib mesylate inhibits the tyrosine-protein kinases Abl, c-Kit and PDGF, as well as the kinase-mediated biochemical events such as MAP kinase activation, inositol phosphate release and cell proliferation. The hallmark of CML is the Philadelphia chromosome, formed by a reciprocal translocation of chromosomes 9 and 22, resulting in a Bcr-Abl fusion protein with enhanced tyrosine kinase activity, dependent on the Abl portion of the protein. The inhibition of Abl tyrosine kinase by imatinib mesylate may interfere with the deregulated myeloid cell proliferation of CML, which Bcr-Abl kinase plays a role in.

SAFETY PHARMACOLOGY:

Neurological effects:

Study BS 30, reviewed within IND[ ]tested CGP 57148B for potential CNS-effects. A single dose of 3, 10 or 30 mg/kg given intravenously resulted in no CNS effects in the mice, based on a CNS-observation rating scale measuring parameters such as tremor, stereotypy, ptosis, and motor function. These same doses did not affect the performance of the mice in a step-through passive avoidance test. Rats administered doses of 3, 10 or 30 mg/kg of CGP 57148B showed no treatment-related effects in the rotarod test or on body temperature. At the 30 mg/kg, a significant prolongation of ethanol-induced sleeping-time was observed. The interaction of this dose with ethanol could be indicative of weak sedative potential of the 30 mg/kg i.v. dose in rats. All doses tested in the rat resulted in a non-dose-dependent decrease in motor activity in a novel environment, also indicative of a mild sedative effect of CGP 57148B.

Cardiovascular effects:

Cardiovascular effects of STI571/CGP 57148B were examined following intravenous administration to the rat in **Project No. 606205**, reviewed in IND[ ]Cardiovascular effects of oral administration of STI571/CGP 57148B in the dog were examined in Test 001091, reviewed here under Special Toxicology.

Intravenous doses of 3, 10 and 30 mg/kg were administered acutely to anesthetized rats. The LD had no effect on cardiovascular parameters. The MD and HD produced a dose-dependent, short-lasting decrease in arterial blood pressure immediately after administration. No effects were seen at any dose on the electrocardiogram.

Drug concentrations of 10, 30 and 100 µM had no effect on the rate of beating or force of contraction in the isolated atria of guinea pigs.

A single oral administration of 100 mg/kg to dogs had no significant effects on blood pressure, heart rate or the electrocardiogram.

Pulmonary effects:

Pulmonary effects of STI571/CGP 57148B were examined following intravenous administration to the rat in **Project No. 606205**, reviewed in IND[ ] Pulmonary effects of oral administration of STI571/CGP 57148B in the dog were examined in Test 001091, reviewed here under Special Toxicology.

Intravenous doses of 3, 10 and 30 mg/kg had no significant effects on the respiratory system in anesthetized rats. Oral administration of 100 mg/kg to dogs also had no significant effects on the respiratory system.

Renal effects:

Renal effects of STI571/CGP 57148B were examined following intravenous administration to the rat in **Project No. 606205**, reviewed in IND[ ]Intravenous doses of 3, 10 and 30 mg/kg had no significant effects on renal function in rats.

Gastrointestinal effects:

DP00-R07: STI571: Safety pharmacology study - Effects on acetic acid-induced stretching, convulsions and gastrointestinal transit. Volume 1.9, page 5-304.

This study was performed by Novartis Pharma K.K., Ibaraki Japan with signed and dated GLP and QA statements included. Doses of 20, 60, 200 and 600 mg/kg were administered orally to mice and its effects on gastrointestinal transit were measured by calculating the thirty minute transit rate of a 5% charcoal suspension administered 2 hours after the test drug administration. The passage rate of the charcoal was not significantly different in any dose group, indicating that in under these conditions, STI571 did not affect gastrointestinal transit.

Abuse liability:

No studies conducted into abuse potential.

Other:

No other safety studies conducted.

Safety pharmacology summary:

CNS-observations were not affected by single i.v. doses of imatinib mesylate up to 90 mg/m^2 in mice. Mild sedative properties could be seen in mice, with ethanol-induced sleeping time significantly prolonged at 90 mg/m^2. Weak sedation was also indicated by a non-dose-dependent decrease in motor activities in rats following imatinib administration. In rats, imatinib at a single i.v. dose of 180 mg/m^2 had no adverse effects on the respiratory or renal systems. However, at doses $\geq$ 60 mg/m^2, imatinib produced a dose-dependent, short-lasting decrease in arterial blood pressure immediately after administration. No effects of imatinib either on the rate of beating or on the force of contraction was seen in the isolated atria of guinea pigs at concentrations of up to 100 μM.

Safety pharmacology conclusions:

No results from the safety pharmacology presented would be cause for concern in the patient population. The mild sedative properties seen in the mouse and rat should not be problematic in the clinical setting. The increased blood pressure was short lasting and with no other cardiovascular effects. No hypertension problems have been seen clinically, however. The safety pharmacology data presented here were obtained with intravenous administration of imatinib. The high dose used in most of the safety pharmacology studies is approximately

equivalent to the human dose on a body surface area basis, when bioavailability (53% in rats) is considered. A toxicology study, reviewed and discussed in the special toxicology section of this review, found no safety issues with the oral route of imatinib, at a dose of 2000 mg/m^2 in the dog, on cardiovascular and respiratory parameters, although this was a single dose administration.

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PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

PK parameters have been determined in the rat, rabbit, dog and monkey. Several studies are reviewed to highlight the PK/TK parameters in the rat and monkey.

Study title: CGP 5714813: A 13-week oral (gavage) toxicity study in rats. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in plasma.

Study no:	**DMPK(US) R98-1782**
Volume #, and page #:	Volume 1.31, page 5-322.
Conducting laboratory and location:	Novartis Corp, East Hanover NJ
Date of study initiation:	20 January 1998
GLP compliance:	Compliance included and signed
QA report:	yes (X) no ( )
Drug, lot #, and % purity:	CGP 57148B, lot# 820296, 98.9% pure
Formulation/vehicle:	Purified water, USP

Dosing:

Species/strain:	Rat/Sprague Dawley
#/sex/group or time point:	10/sex/group
Age:	Approximately 7-8 weeks
Weight:	211.3-258.7g ♂ and 156.8-190.7 g ♀
Doses in administered units:	0, 0.3, 1, 3, and 10 mg/kg/day
Route, form, volume, and infusion rate:	Oral, gavage, 10 mL/kg volume
Sampling schedule:	1, 2, 4, 7 and 24 hrs Day 1/2 and Day 92/93
Analytical method:	

Results:
Exposure in the female rats was higher than in the male rats, with $AUC_{(0-24)}$ values for female rats of 1.3 to 2.6 times higher than in the males. Plasma levels increased overproportionally with the dose of CGP 57148B. With repeated administration over 13 weeks, the exposure to CGP 57148B increased from week 1 to week 13. These data are presented in the following table.

Toxicokinetic Parameters for CGP 57148B in Rat Plasma – Day 1/2 and Day 92/93 of a 13-Week Exposure Schedule

Dose (mg/kg/day)	Sex	$AUC_{(0-24)}$ (ng•h/mL) ± SE		C_{max} (ng/mL)		t_{max} (h)	
		Day 1/2	Day 92/93	Day 1/2	Day 92/93	Day 1/2	Day 92/93
0.3	M	30.0 ± 5.37	46.1 ± 6.22	3.23	3.45	4	4
	F	39.2 ± 3.26	75.9 ± 6.56	5.16	9.12	4	4
1	M	150 ± 6.45	421 ± 55.1	20.8	61.8	4	4
	F	370 ± 2.6	397 ± 76.0	75.6	49.2	4	1
3	M	819 ± 92.1	1790 ± 161	107	217	4	4
	F	2130 ± 362	3030 ± 224	208	494	4	2
10	M	4030 ± 270	9350 ± 835	642	1030	4	4
	F	8580 ± 1190	14500 ± 1210	1101	1290	4	2

Study title: CGP 5714813: A 26-week oral (gavage) toxicity study in rats with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of STI571 in plasma.

This study was reviewed in the Toxicology section under **Test 007033**. Blood was taken from rats in the 26-week toxicity study and toxicokinetic data was obtained. The following table lists the results of the analysis.

Toxicokinetic Parameters for CGP 57148B in Rat Plasma Weeks 1, 4, and 22 of a 26-Week Exposure Schedule

Dose mg/kg/day	Sex	$AUC_{(0-24)}$ (ng•h/mL)			C_{max} (ng/mL)		
		Week 1	Week 4	Week 22	Wk 1	Wk 4	Wk 22
5	M	1328 ± 277	3875 ± 689	6612 ± 535	138	374	796
	F	4628 ± 588	6911 ± 678	8284 ± 299	626	888	1009
15	M	6181 ± 1315	14125 ± 3628	27382 ± 3379	948	1635	2600
	F	15401 ± 2981	29221 ± 2001	39768 ± 6407	1690	3245	3950
50	M	46269 ± 12891	71504 ± 8546	158843 ± 31074	4530	5225	10900
	F	71276 ± 26758	126181 ± 8954	241388 ± 52003	6070	13840	21350

As in the 13-week rat toxicokinetic study, STI571 (CGP 57148B) exposure was greater in the female rats than in the males and was overproportional to dose. Again, accumulation of the drug can be noted by the increased exposure seen in weeks 4 and 22.

Study title: CGP 5714813: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period. Toxicokinetic report: Determination and toxicokinetics of CGP 57148 in monkey plasma.

This study was reviewed in the Toxicology section under **Test 007048**. Blood was taken from the 13-week monkey toxicology study and toxicokinetic parameters determined. The following table lists the results of [ ] analysis.

Mean Toxicokinetic Parameters for CGP 57148B in Monkey Plasma Day 1 and Day 91 of a 13-Week Exposure Schedule

Dose mg/kg/day	Sex	$AUC_{(0-24)}$ (ng•h/mL) ± SD		C_{max} (ng/mL)		t_{max} (h)	
		Day 1	Day 91	Day 1	Day 91	Day 1	Day 91
3	M	214 ± 155	230 ± 107	37.2	32.4	3.33	2.67
	F	218 ± 83.0	75.9 ± 61.1	40.9	44.6	1.67	2.67
15	M	1650 ± 1240	1540 ± 1710	216	176	4.00	2.67
	F	2340 ± 1340	1960 ± 291	310	206	3.33	4.00
75	M	16000 ± 5390	15800 ± 5730	1210	1080	2.67	5.80
	F	15000 ± 4500	15600 ± 4610	1230	1280	4.00	5.20

Unlike in the rat studies, no differences were seen between male and female monkeys with regard to toxicokinetic parameters. Also different from the rat studies is that there is no apparent accumulation in the monkeys following 13 weeks of daily CGP 57148B administration. $AUC_{(0-24)}$ was overproportional to the dose of CGP 57148B.

Absorption:

Pharmacokinetic and toxicokinetic studies addressing absorption were reviewed in the original IND. These data are reported in the PK/TK summary at the end of this section. Studies with Caco-2 cell monolayers **[Study DMPK(CH) R99-1830]** showed imatinib mesylate to have a high intrinsic permeability, predictive of extensive absorption in the human intestinal tract. The sponsor reports that the bioavailability of [^{14}C]imatinib was approximately 53% in the rat, 29-68% in the dog and about 27% in the monkey. The estimation of bioavailability is confounded due to the lack of a dose proportional effect on AUC in test species and the gender differences and drug accumulation observed in the rat. For this reason bioavailability estimations should be viewed with caution. A table follows that contains a compilation of all the PK data, most of which was reviewed in IND [ ] From the results presented, we can see that the rat bioavailability ranges anywhere from 6% (in the male 0.3mg P.O. group) to 82% (in the 50mg P.O. group). In the monkey bioavailability ranges from 19-55%.

Plasma PK parameters [a] for [^{14}C]imatinib in animals and man from single-dose radiolabeled ADM and PK/TK studies

Species (N)	Dose [b] & Route (mg/kg/day)	C_{max} (ng/mL) [b]	t_{max} (h)	AUC (ng/mL)h	$t_{1/2}$ (h)	CL (mL/min/kg)	V_z (L/kg)
Mouse	50 (gavage)	6614	0.17	9	1.3	nd	nd

Rat m, (N=3) [d]	10 (i.v. bolus)	6950	0.08 [c]	17500	4.0	9.5	3.3
m, (N=3) [d]	50 (gavage)	6360	6	71600	4.5	nd	nd
m, (N=3) [d]	100 (gavage)	10600	2	60000 [e]	nd	nd	nd
m+f, (2+2) [d]	0.3 (gavage)	4 [b]	4 [b]	m: 30 [h, i] f: 39 [h, i]	nd	nd	nd
m+f, (2+2) [d]	1 (gavage)	50 [b]	4 [b]	m: 150 [h, i] f: 370 [h, i]	nd	nd	nd
m+f, (2+2) [d]	3 (gavage)	160 [b]	4 [b]	m: 819 [h, i] f: 2130 [h, i]	nd	nd	nd
m+f , (2+2) [d]	10 (gavage)	870 [b]	4 [b]	m: 4030 [h, i] f: 8580 [h, i]	nd	nd	nd
m, (3)	10 (gavage)	241	2	2726 [j]	nd	nd	nd
Rabbit f (8) [d]	10 (gavage)	17000 [j]	2 [j]	11700 [i, j]	nd	nd	nd
f (8) [d]	30 (gavage)	56000 [j]	2 [j]	390000 [i, j]	nd	nd	nd
f (7) [d]	10 (gavage)	126000 [j]	2 [j]	1485000 [i, j]	nd	nd	nd
f (3)	60 (gavage)	53062	3	699826 [j]	nd	nd	nd
Dog m, (N=2)	10 (i.v. bolus)	1510	0.08 [c]	3228	2.8	51.8	10.4
m, (N=2)	10 (capsules)	207	3	879	nd	nd	nd
m, (N=2)	10 (capsules)	2073	4	10785	nd	nd	nd
m+f, (3+3) [d]	10 (capsules)	60 [b]	2	250 [h, i]	nd	nd	nd
m+f, (3+3) [d]	10 (capsules)	450 [b]	2	3040 [h, i]	nd	nd	nd
m+f, (3+3) [d]	10 (capsules)	1410 [b]	4	12400 [h, i]	nd	nd	nd
Cyno monkey m, (N=3)	1 (i.v. bolus)	140	0.08	377	4.2	38.3	11
m, (N=2)	3 (gavage)	69	2	313	2.7	nd	nd
m+f, (3+3) [d]	3 (gavage)	40 [b]	2.5 [b]	216 [h, i]	nd	nd	nd
m+f, (3+3) [d]	15 (gavage)	260 [b]	3.7 [b]	1995 [h, i]	nd	nd	nd
m+f, (3+3) [d]	75 (gavage)	1220 [b]	5.9 [b]	15500 [h, i]	nd	nd	nd
Human HV m (N=4)	200 mg (hard capsule)	923	1.4	9872	13.5	4.18 [l]	4.90 [g]
Patients [d] m+f (total=3)	200 mg (hard capsule)	846 [b]	4 [b]	11.0 [h, i, l] in (µg/mL)h	18.9 [b]	3.0 [l]	3.90 [k]
m+f (total=4)	400 mg (hard capsule)	1908 [b]	3.1 [b]	24.8 [h, i, l]	14.8 [b]	3.0 [l]	3.37 [k]
m+f (total=7)	600 mg (hard capsule)	3395 [b]	2.9 [b]	39.7 [h, i, l]	10.9 [b]	4.0 [l]	3.51 [k]
m+f (total=4)	800 mg (hard capsule)	2315 [b]	14.0 [b]	36.2 [h, i, l]	16.7 [b]	3.0 [l]	4.36 [k]
m+f (total=6)	1000 mg (hard capsule)	3380 [b]	12.2 [b]	51.0 [h, i, l]	11.1 [b]	3.8 [l]	3.24 [k]

nd, not determined; a) All values are mean or average values of N; b) Administered doses are indicated in mg/kg of the methanesulfonic acid salt of imatinib (M,589.72). Cmax, and AUC values refer to the free base form of imatinib (relative molecular mass (M,) 493.61); c) First time point measured; d) PK parameters for unlabeled imatinim; e) AUC(0-8h), at which time point terminal elimination had not started; f) CL/f, apparent clearance where f, the bioavailability, was taken to be 1 and for patients, a weight of 70 kg was used-, g) Vz/f, the apparent terminal volume of distribution, where f, the bioavailability, was taken to be 1; h) value on Day 1; i) AUC(0-24h); j) Value on Day 21; k) Average patient weight taken as 70 kg; l) pg.h/mL; m) b.i.d. regimen.

Distribution:

Study title: DMPK(CH) R00-097: Galactogenic transfer, kinetics and metabolism in milk and plasma after single peroral administration of ^{14}C-labeled ST1571 (100 mg/kg as methanesulfonic acid salt) to lactating rats.

Study no: DMPK(US) R00-097
Volume #, and page #: Volume 1.32, page 5-286.
Conducting laboratory and location: Novartis Pharma AG, Switzerland
Date of study initiation: 22 September 2000
GLP compliance: No compliance included
QA report: yes ( ) no (X)
Drug, lot #, radiolabel, and % purity: STI571, batch RSE 052-9, ^{14}C label, >98% pure
Formulation/vehicle: 0.5% w/w Klucel with 0.1% w/w polysorbate 80

Dosing:

Species/strain:	Rat, lactating – Day 11 after parturition
#/sex/group or time point:	4/timepoint
Age:	Approximately 8-12 weeks
Weight:	240-315 g
Doses in administered units:	100 mg/kg – single dose (19.2 MBq/kg)
Route, form, volume, and infusion rate:	Oral, gavage, 10 mL/kg volume
Sampling schedule:	Milk and blood at 0.5, 2, 4, 8, 24, 48, 72, and 96 hours
Analytical method:	Liquid scintillation counting of total ^{14}C radioactivity

Results:

^{14}C-Pharmacokinetic Parameters of STI571 in Lactating Rats

Dose [mg/kg]	Matrix	^{14}C -t_{max} [h]	^{14}C C_{max} [µmol/L]	^{14}C $AUC_{(0-96)}$ [µmol•h/mL]	Spec. ^{14}C $AUC_{(0-96)}$ [(µmol•h/mL)/mg/kg]
100	Blood	2	23.2	325.1	3.4
	Plasma	2	29.2	380.7	3.9
	Milk	8	95.1	3264	33.7

Data from oral administration of STI571 to lactating rats shows that the t_{max} for ^{14}C concentrations in the blood and plasma is 2 hours. High concentrations were still detected in blood and plasma at 8 hours post administration. At 24 hours, 15-20% of the concentrations at t_{max} was still detected in blood and plasma. ^{14}C transferred to the milk rapidly, as radioactivity was detected at the first time point, 30 minutes after ^{14}C-STI571 administration. Transfer from blood to milk was extensive, as the milk-to-blood ratio was >3 over the entire sampling period. This ratio was maximum toward the end of the sampling, as the ^{14}C concentration in the milk at 24, 48 and 72 hours post administration was 16, 47 and 25 times greater than the ^{14}C concentration in the blood at these same time points, respectively. These data do not distinguish between STI571 and any radiolabeled metabolite. These results do indicate the potential for nursing infants to be exposed to imatinib mesylate and/or its metabolites if a patient were to breastfeed while taking Gleevec®.

Study title: Quantitative) in female normal and bearing C6 tumors BALB/c nu/nu mice following a 50 mg/kg po dose of [^{14}C]ST1571.

Study no:	**DMPK(US) R00-1004**
Volume #, and page #:	Volume 1.33, page 5-26.
Conducting laboratory and location:	Novartis Pharma AG, Switzerland
Date of study initiation:	June 2000
GLP compliance:	No
QA report:	yes ( ) no (X)
Drug, lot #, and % purity:	STI571, batch RSE 052-9, ^{14}C label, >98% pure
Formulation/vehicle:	Dulbecco's phosphate buffered saline

Dosing:

Species/strain:	Mice/BALB/c *nu/nu* w/ and w/o C6 tumors
Age:	Approximately 7-8 weeks
Weight:	20-22g w/o tumors and 20-25 w/
Doses in administered units:	50.2-51.2 mg/kg of [^{14}C]ST1571
Route, form, volume, and infusion rate:	Oral, gavage, 20 mL/kg volume
Sampling schedule:	0.5, 2, 4, 10, 24 and 72 hrs
Analytical method:	Quantitative

Results:

Results of the (show little brain distribution. Tissues with the highest levels of radioactivity are the liver, kidney, lung, exocrine glands and intestinal wall. Distribution in the normal and tumor bearing mice are similar. Residual radioactivity in the tumor bearing mice is lower at 72 hrs than in the normal mice. Though in the 2-24 hr period the radioactivity is higher in the tumor bearing mice, perhaps due to a slower elimination in these mice compared to the normal mice. There was moderate uptake of radioactivity into the primary tumors but greater uptake by metastatic tumors. The table below shows the tissue concentrations of radioactivity in the tumor bearing mice.

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Table 5.2: Tissue concentrations of radioactivity in mice bearing C6 tumors

Tissue radioactivity concentrations in female mice bearing C6 tumors at 30 min and 2, 4, 10, 24 and 72 h after a 50 mg/kg po dose of [^{14}C]STI571; n=1 mouse per time point

Tissues (nmol/g)	30min	2h	4h	10h	24h	72h
Adrenal (cortex)	124.06	75.54	27.22	38.10	11.66	0.81
Adrenal (medulla)	256.10	176.72	61.15	71.32	17.66	0.79
Adrenal (zona reticularis)	327.21	311.06	152.49	270.51	87.30	5.76
Bile	877.34	1456.20	1140.52	533.93	509.42	nd
Blood	78.06	44.70	17.87	19.69	3.56	nd
Blood vessel wall	97.57	62.13	19.71	25.65	5.48	nd
Bone marrow	118.32	109.26	30.47	34.92	7.17	nd
Bone mineral	19.53	5.03	2.01	2.73	T	nd
Brain	4.86	2.94	1.45	1.85	T	nd
Brown fat	115.60	64.70	26.40	40.99	13.12	nd
Choroid plexus	49.92	15.80	10.03	7.89	2.29	nd
Ear	35.36	62.80	18.37	20.96	6.20	nd
Eye (lens)	1.30	2.18	1.09	1.28	0.81	nd
Eye (ocular membranes)	48.11	51.75	22.14	17.88	7.35	nd
Eye (vitreous body)	1.89	1.24	1.13	1.51	0.52	nd
Harderian gland	220.36	125.44	60.60	63.06	34.40	nd
Heart	90.72	44.40	15.99	15.23	3.61	nd
Intestinal wall (colon)	113.20	68.13	96.17	50.08	39.93	nd
Intestinal wall (duodenum)	216.39	102.22	46.90	71.58	18.77	nd
Kidney (CM junction)	363.79	242.98	90.97	159.01	42.23	nd
Kidney (cortex)	233.40	131.39	44.31	50.76	17.03	nd
Kidney (medulla)	189.65	95.83	43.42	87.18	13.48	nd
Kidney (pelvis)	497.95	316.32	156.45	130.74	22.86	nd
Lachrymal gland	207.74	143.47	68.10	54.67	32.86	nd

nd: below detection limit (0.18 nmol/g); T (traces): between detection limit and quantitation limit
nm: not measured; ns: no sample

Table 5.2 cont'd: Tissue concentrations of radioactivity in mice bearing C6 tumors

Tissue radioactivity concentrations in female mice bearing C6 tumors at 30 min and 2, 4, 10, 24 and 72 h after a 50 mg/kg po dose of [^{14}C]STI571; n=1 mouse per time point

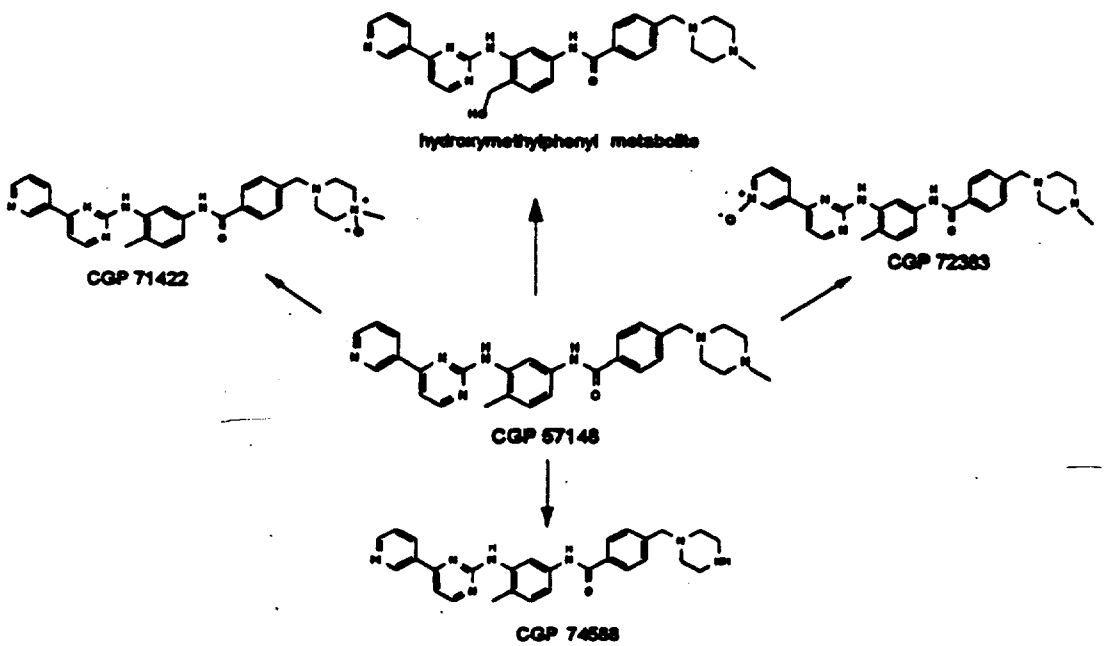
Tissues	30min	2h	4h	10h	24h	72h
Liver	266.86	152.60	53.86	75.04	20.70	0.97
Lung	140.29	87.77	28.99	31.23	7.02	nd
Muscle	40.13	26.06	5.55	7.64	1.16	nd
Pancreas	239.97	107.66	36.43	53.46	26.46	nd
Pituitary gland	212.16	105.04	64.12	30.86	14.53	nd
Ribs	19.58	16.80	6.74	8.06	1.50	nd
Salivary gland	199.35	121.70	46.43	58.52	20.16	nd
Skin	46.47	46.96	28.94	33.11	6.66	T
Spleen (red pulp)	293.45	204.37	ns	55.44	32.92	nd
Spleen (white pulp)	293.45	121.46	ns	55.44	22.76	nd
Stomach (glandular)	160.83	47.99	52.75	37.24	27.53	nd
Stomach (non glandular)	nd	29.67	28.71	28.32	5.80	nd
Thyroid gland	114.69	239.86	26.74	26.25	8.52	nd
Tongue	86.59	55.22	14.67	17.97	2.80	nd
White fat	67.67	9.62	4.20	8.12	2.45	nd
Tumor (metastase)	41.30	132.54	89.01	86.16	27.40	1.07
Tumor (liquid)	2.07	16.40	15.37	16.23	4.82	nd
Tumor (solid)	7.75	34.43	23.21	23.39	5.24	nd

nd: below detection limit (0.18 nmol/g); T (traces): between detection limit and quantitation l
nm: not measured; ns: no sample

Metabolism:

Studies using liver S12 fractions show that CYP3A4 was the major human P450 enzyme involved in the metabolism of imatinib mesylate **[Study DMPK(CH) 1997/564]**. Additional studies reviewed in IND [ ] indicate that the biotransformation of [^{14}C]-imatinib follows the same metabolic pathway in rat, dog and man. The main metabolite produced in human liver S12 incubation was CGP 74588, the *N*-desmethyl derivative of the parent compound. Both rat and dog liver S12 produced CGP 71422, the piperazine *N*-oxide of CGP 57148B **[Studies DMPK(CH) 1997/038 and DMPK(CH) 1997/355]**.

The structures for major metabolites produced after a single 10 mg/kg per oral dose to rats and dogs are shown in the following figure:



Testing a panel of potential comedications for potential interactions showed fluconazole and erythromycin to inhibit imatinib metabolism.

Excretion:

The predominant route of elimination of radioactivity following administration of [14C]CGP 57148B to rats and dogs was fecal **[Study DMPK(CH) 1997/232]**. Unchanged imatinib accounted for 45%, 47% and 31% of the fecal radioactivity in rats, dogs and monkeys, respectively. Urinary radioactivity seen in these animals was 40% unchanged imatinib. Seven days after drug administration virtually all of the imatinib was recovered in feces and urine in the

monkey and dog. In the rat less than 0.5% of the radioactive dose remained one week after dosing.

Excretion of imatinib and total radioactivity following a single dose of radiolabeled imatinib

Species	Dose (mg/kg)	Dose Route	Amount Excreted (% of Dose)					
			Urine			Feces		
			Radioactivity		Imatinib	Radioactivity		Imatinib
			0-24h	0-168h	0-168h	0-24h	0-168h	0-168h
Rat	10	I.V.	8.70	9.68	3.4 [a]	83.14	90.37	39.1 [a]
	10	P.O.	7.82	9.21	3. 0 [a]	85.98	96.34	48.7 [a]
	60	P.O.	10.11	11.55	2.5 [a]	75.03	85.20	38.5 [a]
Dog	10	I.V.	1.26 [b]	2.30	0.5 [b]	87.73 [c]	91.05	39.4 [c]
	10	P.O.	1.98 [b]	3.86	0.7 [b]	92.41 [c]	95.79	37.1 [c]
	50	P.O.	2.85	6.10	1.5 [a]	88.41 [c]	94.91	46.0 [c]
Cynomolgus monkey	1	I.V.	0.13	0.24	nd	70.3 [e]	76. 1 [d]	21.7 [e]
	3	P.O.	0.80	0.94	nd	86.7 [e]	96.9	12.8 [e]
Man	200	P.O						

a) 0-24 hours; b) 0-8 hours; c) 0-72 hours-, d) total radioactivity recovery in urine and feces was 77.2% of the dose; e) 0-48 hours; nd: not detected, LOQ

Other studies:
No other studies reviewed.

PK/TK summary:

The table below summarizes the PK parameter data obtained in the animal studies and in humans. Gender differences were seen in the rat, but not in other laboratory animals. Drug accumulation over repeated dosing was only evident in the rat. Placental transfer of imatinib has been observed in laboratory animals, as has transfer to the milk of lactating rats.

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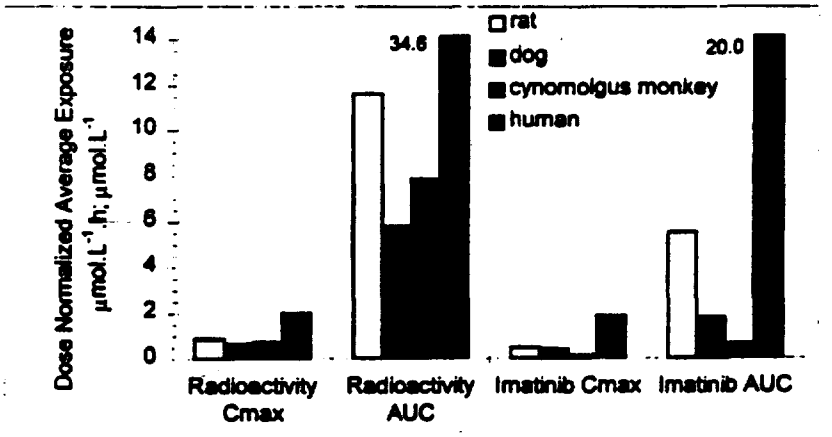
Pharmacokinetic parameters of total ^{14}C substances in plasma of animals and man						
Species	Gender (N)	Dose[a] (mg/kg)	Route	^{14}C-AUC [(ng-eq/mL)h][b]	^{14}C-C_{max} (ng-eq/mL)[b]	Absorption ^{14}C substance[b]
Rat	m (3)	10	I.V.	12686 [c]	4590	
	m (3)	10	P.O.	6762 [d]	543	53%
	m (3)	60	P.O.	121426 [d]	8144	
Rabbit	f (3) pregnant	60	P.O.	1323786 [e]	113034	
Dog	m (2)	10	I.V.	7108 [f]	1698	
	m (2)	10	P.O.	2863 [g]	326	45% [j]
	m (2)	50	P.O.	33269 [g]	2498	
	m (1)	100	P.O.	62687 [e]	4556	75%
Cynomolgus monkey	m (3)	1	I.V.	121 0 [h]	262	
Human	m (3)	3	P.O.	3880 [h]	368	
	m (4)	200 mg	P.O.	17079 [i]	997	

a) Administered doses are indicated in mg/kg of the methanesulfonic acid salt of imatinib (M,589.72). C_{max} and AUC values are given in equivalents relative to the free base form of imatinib (relative molecular mass (M_r) 493.61); b) Average of N; c) AUC(O.08-72h); d) AUC(O-72h); e) AUC(O-24h),mean of 2 rats; f) AUC(O.08-48h); g) AUC(O-48h); h) AUC(O-168h); i) AUC(O-48h); j) the actual dose of one dog was 8.1 mg/kg

Figure 2: Plasma Cmax and AUC of total radioactivity and imatinib



The dose of mesylate salt to rats was 10 mg/kg (5), to dogs was 10 mg/kg (4) and to cynomolgus monkeys was 3 mg/kg (11). The dose in the human ADME study was 3.16 mg/kg of mesylate salt (the average weight was 75 kg) (12).

AUC values were calculated over the time invervals 0-48h (14C rats), 0-24h (imatinib rats), 0-48h (dogs), 0-168h (cynomolgus monkeys), and 0-48h (humans).

PK/TK conclusions:

The pharmacokinetic data in the human is similar to that seen in the animal studies. More extensive protein binding is seen in the human, primarily to albumin and α-1-acid glycoprotein (AAG), which would account for the greater Cmax and AUC values seen in humans. Absorption of the drug was extensive with distribution primarily to the liver, kidney, lungs, exocrine glands and colon. The primary metabolite of imatinib in humans is CGP 57148, formed by the N-demethylation at the piperazine 4-nitrogen of imatinib. CYP3A4 was the major human cytochrome P450 enzyme involved in the biotransformation of imatinib. Placental transfer of [^{14}C]imatinib was demonstrated in the rat and rabbit, as was transfer of radioactivity into the milk of lactating rats. The majority of the drug is eliminated unchanged via the biliary route and elimination is essentially complete. In the human data presented, at 168 hrs only 80% of the radioactivity is accounted for in the urine and feces. This could be due to a slower rate of fecal excretion, or to subject compliance in collecting the urine and feces samples.

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TOXICOLOGY:

Study title: STI571: 26-week oral (gavage) toxicity study in rats with a 4-week recovery period.

Key study findings: The NOAEL from this study was 5 mg/kg/day for 26-week oral administration. Higher doses yielded slight myelosuppression and elevated liver function tests.

Study no:	Test 007033
Volume #, and page #:	Volume 1.15, page 5-1
Conducting laboratory and location:	Novartis Pharmaceuticals Corp., East Hanover, NJ
Date of study initiation:	3 March 2000
GLP compliance:	Compliance included and signed
QA report:	yes (X) no ( )
Drug, lot #, and % purity:	STI571 mesylate, lot# 9923006, 99.9% pure
Formulation/vehicle:	Purified water, USP

Methods (unique aspects): No unique aspects

Dosing:

Species/strain:	Rat/Sprague Dawley
#/sex/group or time point:	20/sex/group
Satellite groups used for toxicokinetics or recovery:	10/sex for control and high dose groups – recovery animals
Age:	Approximately 6-8 weeks
Weight:	180.2-223.2g ♂ and 151.7-188.5 g ♀
Doses in administered units:	0, 5, 15 and 50 mg/kg/day
Route, form, volume, and infusion rate:	Oral, gavage, 5 mL/kg volume

Observations and times:

Clinical signs:	Twice daily on weekdays, once on weekends
Body weights:	Weekly for weeks 1-14, every two weeks for weeks 16-26, weekly during recovery
Food consumption:	Weekly for weeks 1-14, every two weeks for weeks 16-26, weekly during recovery
Ophthalmoscopy:	Once for all animals pretest; then surviving control and high dose animals in weeks 13 and 26
EKG:	None
Hematology:	On last 10 surviving animals in weeks 14, 25 and late in the recovery period
Clinical chemistry:	On last 10 surviving animals in weeks 14, 25 and late in the recovery period
Urinalysis:	On last 10 surviving animals in weeks 14, 25 and late in the recovery period

Gross pathology: At necropsy – after 26 weeks for most animals, 30 weeks for recovery animals

Organs weighed: Adrenals, brain, heart, kidney, liver, ovary, pituitary, prostate, spleen, testis, thymus, thyroid, uterus

Histopathology: At necropsy – after 26 weeks for most animals, 30 weeks for recovery animals

Toxicokinetics: From 10 rats/sex/group on days 1, 2 and weeks 4 and 22. 2 rats/sex/group at 1, 2, 4, 6 and 24 hours post dosing

Other: None

Results:

Mortality: Control ♂ - brain neoplasm
LD ♂ - salivary neoplasm
2HD ♂ - no cause of death determined; clinical signs included red ears, red substance in mouth, swollen muzzle, chromodacryorrhea
HD ♀ - gavage accident

Clinical signs:

Clinical Signs	Dose		
Male rats	**LD**	**MD**	**HD**
Salivation and oral red substance	2/20	13/20	30/30
Prominent eyes, wet perineal staining, chromodacryorrhea, red penile discharge		10/20	30/30
Red ears, squinting, swollen appendage, red feet, dry perineal staining, blood/dark yellow urine on cage paper, chromorhinorrhea, swollen muzzle, dry stained fur			30/30
Clinical Signs	**Dose**		
Female rats	**LD**	**MD**	**HD**
Chromodacryorrhea	6/20	2/20	22/30
Prominent eyes, oral red substance		5/20	29/30
Swollen appendage, limping, red feet, dry perineal staining, swollen muzzle			30/30

Body weights: HD ♀ rats during recovery period – decreased weights when compared to control; 9-15% ↓ weight

Food consumption: No treatment-related changes

Ophthalmoscopy: No treatment-related changes

Electrocardiograph: Not conducted

Hematology: [redacted]

	Male		Female	
	MD	HD	MD	HD
WBC count				
Week 14	—	—	—	↑41%
Week 26	—	—	—	↑35%
End of Recovery	—	—	—	—
Neutrophils				
Week 14	↓43%	↓47%	—	↑45%
Week 26	—	↓35%	—	↑44%
End of Recovery	—	—	—	—
Eosinophils				
Week 14	—	—	—	↓43%
Week 26	—	↓51%	—	↓56%
End of Recovery	—	—	—	—
RBCs				
Week 14	↓5%	↓26%	—	↓28%
Week 26	↓8%	↓32%	—	↓36%
End of Recovery	—	↓16%	—	↓12%
Platelets				
Week 14	—	—	—	—
Week 26	↓25%	↓29%	—	—
End of Recovery	—	↓25%	—	—
Hematocrit				
Week 14	—	↓12%	—	↓17%
Week 26	—	↓16%	—	↓24%
End of Recovery	—	↓7%	—	—
Hemoglobin				
Week 14	—	↓9%	—	↓14%
Week 26	—	↓13%	—	↓20%
End of Recovery	—	—	—	—
MCV				
Week 14	↑4%	↑18%	—	↑15%
Week 26	↑7%	↑22%	—	↑18%
End of Recovery	—	↑11%	—	↑9%
MCH				
Week 14	↑6%	↑23%	—	↑19%
Week 26	↑8%	↑27%	—	↑24%
End of Recovery	—	↑16%	—	↑11%
MCHC				
Week 14	—	↑4%	—	↑4%
Week 26	—	↑4%	—	↑5%
End of Recovery	—	↑4%	—	↑2%
RBC Dist. Width				
Week 14	—	—	—	↑8%
Week 26	—	—	—	↑10%
End of Recovery	—	↑11%	—	↑6%

Clinical chemistry:

Clinical Chemistry - Compared to Control				
	Male		Female	
	MD	HD	MD	HD
AST				
Week 14	—	↑40%	—	↑40%
Week 26	—	↑60%	—	↑60%
End of Recovery	—	—	—	—
ALT				
Week 14	—	↑23%	—	↑23%
Week 26	—	↑32%	—	↑32%
End of Recovery	—	↓26	—	↓26
Total Protein				
Week 14	—	—	↑8%	↑12
Week 26	—	↑7%	—	↑8%
End of Recovery	—	—	—	—
Albumin				
Week 14	—	—	—	↑15%
Week 26	—	↑9%	—	↑9%
End of Recovery	—	—	—	—
Globulins				
Week 14	—	—	—	—
Week 26	—	—	—	↑19%
End of Recovery	—	—	—	↑17%
AG ratio				
Week 14	—	—	—	—
Week 26	—	—	—	↓13%
End of Recovery	—	—	—	↓22%
Sodium				
Week 14	—	—	—	↓1.4%
Week 26	—	—	—	—
End of Recovery	—	—	—	—
Cholesterol				
Week 14	—	—	—	↓46%
Week 26	—	—	—	↓53%
End of Recovery	—	—	—	—
Triglycerides				
Week 14	—	—	—	↓38%
Week 26	—	—	—	—
End of Recovery	—	—	—	—

Urinalysis: No treatment-related changes

Organ weights:

Organ Weight Changes – Compared to Control				
	Males		Females	
	MD	HD	MD	HD
Heart				
Week 26	↑13%	↑37%	—	↑24%
Spleen				
Week 26	↓10%	↓18%	—	—
Adrenal				
Week 26	—	↑29%	—	↑61%
End of Recovery	—	—	—	↑27%
Liver				
Week 26	—	↑13%	—	—
Thyroid				
Week 26	—	↑24%	—	—
Ovary				
Week 26	—	—	—	↑202%
End of Recovery	—	—		↑52%
Pituitary				
Week 26			—	↓20%
Testis				
Week 26	—	↓12%	—	—

Gross pathology: HD rats – enlarged masseter muscles; dark or red ovarian nodules in ♀ rats – also seen in HD recovery animals

Histopathology:

Significant Histopathological Changes – Compared to Control		
Organ/Tissue Finding	**HD – Week 26**	**HD – Recovery**
Ovaries		
Hemorrhagic corpora lutea	20/20	5/10
Cystic corpora lutea	7/20	2/10
Hemosiderophages	19/20	10/10
Muscle	21/22 ♂	3/8 ♂
Hypertrophy, masseter	15/20 ♀	2/8 ♀
Lungs	12/22 ♂	8/8 ♂
Macrophage, foamy	15/20 ♀	4/10 ♀
Mesenteric lymph nodes	11/22 ♂	6/8 ♂
Eosinophilic macrophages	8/20 ♀	7/10 ♀
Harderian glands	13/22 ♂	1/8 ♂
Atrophy of acinar cells	15/20 (4/20MD) ♀	3/10 ♀
Adrenal cortex		
Focal angiectasis	14/20 ♀	
Renal pelvic epithelium	14/22 ♂	
Hyperplasia	12/20 (6/20MD) ♀	6/10♀
Focal mineralization	6/20 ♀	
Bone marrow	8/22 (1/20MD) ♂	
Small foci of fibrosis	8/20 (2/20MD) ♀	
Bone	4/22 ♂	
New bone formation	6/20 ♀	

Toxicokinetics:

Table 2.1-2. Dose normalized TK parameters

Week	Dose (mg/kg/day)	Gender	Dose normalized AUC_{0-24} (ng•h/mL)/(mg/kg/day)	Dose normalized C_{max} (ng/mL)/(mg/kg/day)
1	5	Male	288	27.6
		Female	826	125
	15	Male	412	63.2
		Female	1027	113
	50	Male	925	90.6
		Female	1426	121
4	5	Male	776	74.8
		Female	1382	176
	15	Male	942	109
		Female	1946	216
	50	Male	1430	106
		Female	2624	277
22	5	Male	1322	189
		Female	1657	202
	15	Male	1825	173
		Female	2661	283
	50	Male	3177	218
		Female	4828	427

Figure 2.1-1. AUC_{0-24} vs Dose

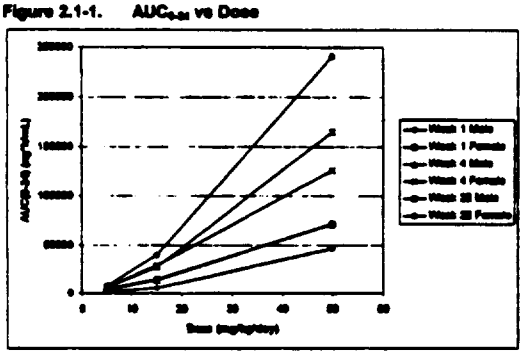
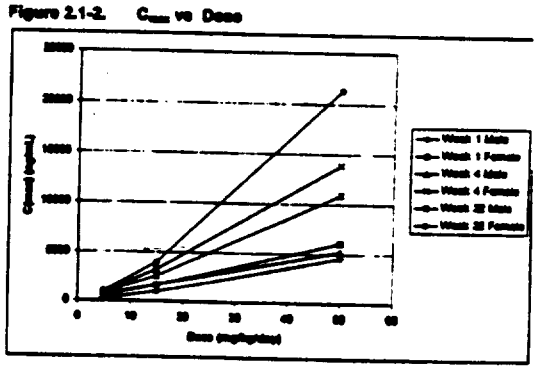


Figure 2.1-2. C_{max} vs Dose



Summary of individual study findings:

Approximately three percent of the HD group rats, two of the 60 rats treated with 50 mg/kg/day, appear to have died due to the treatment drug. While no cause of death was determined, the clinical signs these rats exhibited prior to death were those seen more frequently in the higher dose animals when compared to control. No treatment related lethality was seen at the 15 or 5 mg/kg/day doses. The hematological and clinical chemistry effects of 26-week administration of imatinib in the rat is consistent with what was seen following 13-week administration. Myelosuppression, as well as elevated liver function tests, were seen in a dose-dependent manner, but primarily at the highest dose. The LD rats did not exhibit any of these effects.

The LD rats also did not show significant effects of the test article on organ weights, gross pathology, or histopathology. Organ weight changes that were seen in MD and HD rats had no correlating histopathological changes associated with them except in the female rats' adrenals and ovaries. The histopathological changes were primarily changes seen spontaneously in rats, but with an increased incidence in the treated animals.

The toxicokinetics data indicates that the STI571 AUC and C_{max} values for the female rats were higher than were those of the male rats at the same time-period and drug dose. In

addition, dosing over a 22-week period also increased these two values in both male and female rats, suggestive of drug accumulation.

The medium and high doses tested in this study were associated with a variety of clinical and toxicological changes, many of which had either reversed or were lessened at the 4-week recovery time point. The low dose, 5 mg/kg/day, yielded minimal clinical signs of toxicity and for this study is the NOAEL of STI571.

Study title: A 13-week oral (gavage) toxicity study in cynomolgus monkeys with a 4-week recovery period.

Key study findings: The NOAEL in this study was 15 mg/kg/day. This dose was well tolerated. The HD of 75 mg/kg/day for 13 weeks caused hematological changes and clinical signs of toxicity.

Study no:	987003
Volume #, and page #:	Volume 1.22, page 5-1
Conducting laboratory and location:	Novartis Pharmaceuticals Corp., East Hanover, NJ
Date of study initiation:	17 Dec 1997
GLP compliance:	Compliance included and signed
QA report:	Yes (X) no ( )
Drug, lot #, and % purity:	CGP 57148B (STI571), lot# 820396, 99.0% pure
Formulation/vehicle:	Purified water, USP

Methods (unique aspects): No unique aspects

Dosing:

Species/strain:	Monkey/Cynomolgus
#/sex/group or time point:	3/sex/group
Satellite groups used for toxicokinetics or recovery:	2/sex for control and HD for recovery
Age:	Approximately 2 - 6.5 years
Weight:	3.6 – 5.2 kg ♂ and 2.6 – 4.2 kg ♀
Doses in administered units:	0, 3, 15, and 75 mg/kg/day
Route, form, volume, and infusion rate:	Oral, gavage, 5 mL/kg volume

Observations and times:

Clinical signs:	Once daily pre-test and recovery; at least 2 times daily during dosing
Body weights:	Once weekly during dosing and recovery
Food consumption:	Estimated daily
Ophthalmoscopy:	During pretest, week 7 and end of dosing
EKG:	Pretest and week 1, 6, 8 and 13
Hematology:	Pretest and weeks 5, 9, 13, and recovery week 4
Clinical chemistry:	Pretest and weeks 5, 9, 13, and recovery week 4
Urinalysis:	Pretest and weeks 5, 9, 13 and recovery week 4
Gross pathology:	At scheduled sacrifice – end of 13 weeks or after 4 weeks recovery

for 2/sex/dose for control and HD monkeys

Organs weighed: Adrenal, brain, heart, kidney, liver, ovary without oviduct, pituitary, prostate, spleen, testis without epididymis, thyroid with parathyroid, uterus

Histopathology: At scheduled sacrifice – end of 13 weeks or after 4 weeks recovery for 2/sex/dose for control and HD monkeys

Toxicokinetics: Week 1 (days 1 and 2) and week 13 (days 91 and 92)

Results:

Mortality: No mortality

Clinical signs:

Frequency of Clinical Signs

	75 mg/kg		75 mg/kg- recovery	
Emesis	5/5 ♂	4/5 ♀	—	—
Pale skin	3/5 ♂	4/5 ♀	2/2 ♂	2/2 ♀
Pale gums	3/5 ♂	3/5 ♀	1/2 ♂	2/2 ♀

Body weights: HD - 2/5 ♀ and 2/5 ♂ - 5-10% ↓ body weight for first 3 weeks
After week 3, all but 1/5 ♀ gained weight
HD 1/5 ♀ - weight at week 13 was ↓7% from weight at start
No body weight effects seen during recovery

Food consumption: HD 3/5 ♂ and 3/5 ♀ - consumed less than 25% of the food given

Ophthalmoscopy: No treatment-related effects

Electrocardiography: No treatment-related effects

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